Complete Summary

GUIDELINE TITLE

Benefits and risks of controlling blood glucose levels in patients with type 2 diabetes mellitus.

BIBLIOGRAPHIC SOURCE(S)

American Academy of Family Physicians, American Diabetes Association. Controlling blood glucose levels in patients with type 2 diabetes mellitus. J Fam Pract 2000 May;49(5):453-60. [110 references]

American Academy of Family Physicians. The benefits and risks of controlling blood glucose levels in patients with type 2 diabetes mellitus. A review of the evidence and recommendations American Academy of Family Physicians, American Diabetes Association. Leawood (KS): American Academy of Family Physicians (AAFP); 1999 Apr.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Type 2 diabetes mellitus

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Prevention
Risk Assessment

CLINICAL SPECIALTY

Endocrinology
Family Practice
Internal Medicine
Preventive Medicine

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To outline the benefits and risks of controlling blood glucose levels in patients with type 2 diabetes mellitus

TARGET POPULATION

Adult patients with type 2 diabetes mellitus

INTERVENTIONS AND PRACTICES CONSIDERED

Glycemic control

MAJOR OUTCOMES CONSIDERED

- Incidence and progression rates of microvascular complications of type 2 diabetes mellitus, including retinopathy, nephropathy, and neuropathy.
- Incidence of macrovascular complications of type 2 diabetes mellitus, including heart disease, stroke, and peripheral vascular disease.
- All-cause mortality rates
- Incidence of adverse effects associated with glycemic control

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The literature review sought published evidence regarding the effects of glycemic control on microvascular and macrovascular complications in type 1 and type 2 diabetes and on the incidence of adverse effects. A manual and computerized search were conducted. In the first phase, relevant articles were identified by examining the reference lists of recent review articles, supplemented by citations

noted in the articles retrieved and by suggestions from panel members and experts. In the second phase, a computerized search was conducted to identify articles, especially recent publications, not uncovered by the manual search. The MEDLINE search sought all English-language publications during 1990-1997 involving human subjects and indexed by one of the following MeSH terms: DIABETIC--ANGIOPATHIES, DIABETIC--NEPHROPATHIES, DIABETIC--NEUROPATHIES, DIABETIC--RETINOPATHIES. Two panel members independently reviewed the search results, and all articles selected by either panel member were pulled. A total of 1583 citations were recorded and 798 articles retrieved. Selected articles published after March 1997 were reviewed during the course of the panel´s work.

NUMBER OF SOURCE DOCUMENTS

A total of 1583 citations were recorded and 798 articles retrieved.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Subjective Review

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

The panel developed its recommendations directly from the evidence, giving greater weight to evidence from clinical trials than to evidence from observational studies. Letter codes for grading the strength of recommendations (e.g., "A" for recommendations based on clinical trial evidence) were not employed so that narrative descriptions could be used to more fully characterize the evidence.

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

All articles retrieved in the manual search underwent critical appraisal using a review form that identified relevant outcome data and assessed study design and quality. The forms collected information to select studies with relevant data to be transferred to evidence tables. Studies subsequently identified in the computerized search were reviewed by staff, and relevant data were added to the evidence tables.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Other

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The panel developed its recommendations directly from the evidence, giving greater weight to evidence from clinical trials than to evidence from observational studies. Letter codes for grading the strength of recommendations (e.g., "A" for recommendations based on clinical trial evidence) were not employed so that narrative descriptions could be used to more fully characterize the evidence.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

The guideline developers reviewed cost analyses.

Intensive glycemic control generally requires patients to closely monitor their blood glucose levels at home, often on a daily basis; follow careful dietary restrictions and increased physical activity; tolerate minor side effects and the risk of more serious complications from medications; visit the doctor on a regular basis for testing and examinations; and absorb out-of-pocket costs not covered by insurance for physician services and medical supplies, lost work (or school) time, and transportation. Although the influence attributable to insulin versus glycemic control is unclear, a cohort study found that insulin users had more laboratory tests performed, 2.4 more outpatient visits per year, and almost 300 more fingersticks for home glucose monitoring than patients using sulfonylureas. In many cases these inconveniences, discomforts, and costs must be borne over a number of years, often a lifetime. There are currently few reliable data on which to measure the magnitude of these problems, their relative importance to patients, or the degree to which they are offset by the benefits of treatment. The DCCT found no association between intensive treatment and lower quality of life. A recent study suggested that the net effect of improved glycemic control is improved quality of life and work productivity and decreased absenteeism and unemployment.

METHOD OF GUIDELINE VALIDATION

External Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The report was reviewed by a panel of outside experts and family physicians, and revisions consistent with the panel methodology were incorporated. The final report was approved in March 1999 by the respective Boards of the American Academy of Family Physicians and the American Diabetes Association

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The evidence demonstrates a continuous and curvilinear relationship between hyperglycemia and the microvascular and neuropathic complications of diabetes, with risk rising progressively as mean blood glucose concentrations increase. The

data indicate that patients with type 2 diabetes benefit from the control of blood glucose levels. The potential magnitude of absolute risk reduction varies as a continuous variable, however, depending on: the (a) patient´s current glycated hemoglobin level and (b) duration and magnitude of prior hyperglycemia; and (c) extent of preexisting microvascular complications. A critical variable is the patient´s glycated hemoglobin level; individuals with marked elevations generally benefit more (in reduced absolute risk of complications) from the same absolute reduction in glycated hemoglobin levels than do individuals with mild-moderate elevations. The probability that the patient will live long enough to experience the benefits of reduced complications depends on (d) cardiovascular risk factors other than blood glucose (e.g., tobacco use, blood pressure, serum lipid levels, physical activity, obesity, preexisting coronary artery disease) and (e) other determinants of life expectancy (e.g., age, coexisting diseases, health status).

The evidence demonstrates that, for an individual with type 2 diabetes, the better the glycemic control, the lower the probability of developing chronic microvascular and neuropathic complications (and, possibly, cardiovascular complications). However, because of differences in patients´ life expectancies and comorbidities, it is inappropriate to set a uniform target glycated hemoglobin level for all patients with type 2 diabetes. Individuals with long life expectancies and few comorbidities may wish to pursue euglycemia, but less vigorous goals may be appropriate in elderly individuals with multiple comorbid conditions and/or limited life expectancies.

Whether the magnitude of benefit of a given treatment goal justifies the potential inconvenience, harms, and costs involves value judgments that must be tailored to the individual patient. Patients´ personal risk profiles and capabilities and the relative importance they assign to the potential outcomes and supporting evidence are integral to determining how intensively to treat. Cardiovascular disease is the most likely cause of death in patients with type 2 diabetes, and thus attention to glycemic control should not distract clinicians and patients from other interventions that may be far more effective in preventing coronary artery disease and stroke, such as smoking cessation, serum lipid management, control of blood pressure, diet, physical activity, and weight management. Guidelines for the detection and management of these risk factors are published elsewhere. Clinicians should also give due attention to treatments other than glycemic control for preventing microvascular complications (e.g., blood pressure control and use of angiotensin converting enzyme inhibitors for diabetic nephropathy).

Regardless of the treatment goal and of choices about the intensity of glycemic control, patients face considerable barriers in implementing recommendations to modify diet and other personal lifestyle habits; comply with self-monitoring, medication, and home care instructions; and return for follow-up visits. Physicians should work with patients to identify and design solutions for remediable barriers and should utilize recommended techniques for patient education and counseling to give patients the factual information and motivational encouragement they need for meaningful change.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The evidence for the association of glycemic control and specific microvascular and macrovascular complications is divided into three categories: observational evidence in type 2 diabetes, clinical trial evidence in type 2 diabetes, and clinical trial evidence in type 1 diabetes.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

A strong body of evidence suggests that the incidence of microvascular complications can be reduced significantly by therapeutic measures to lower blood glucose to normal or near-normal levels. A seminal study was the Diabetes Control and Complications Trial (DCCT), published in 1993, which showed in a sample of 1441 patients with type 1 diabetes that a program of intensive glycemic control could lower the incidence of retinopathy, nephropathy, and neuropathy by 76%, 44%, and 69%, respectively, over a mean period of 6.5 years. In 1998, a landmark British trial involving 4200 patients with type 2 diabetes (the United Kingdom Prospective Diabetes Study [UKPDS]) reported that the 10-year incidence of microvascular complications was 25% lower in patients who were intensively treated with diet and medications than in those receiving conventional treatment.

Although several observational studies have shown a correlation between hyperglycemia and mortality, there is only limited evidence that glycemic control can reduce the risk of macrovascular complications. The UKPDS reported a 16% reduction in myocardial infarction of borderline statistical significance. One clinical trial found that improved glycemic control (with insulin in patients with myocardial infarction) significantly reduced the incidence of ischemic cardiac events, stroke or cardiovascular deaths. Two others may have lacked adequate duration or sample size to detect an effect.

Different kinds of patients with type 2 diabetes will benefit differently from improved glycemic control. The probability of benefit for each of the different subgroups of patients, and their clinical importance to the individual, must be weighed against the potential life disruption, adverse effects of treatment, and monetary and non-monetary costs in order to fully assess the benefit-risk ratio.

Considerations for applying the results of the clinical studies to routine practice and the patient-specific factors that influence the magnitude of benefit expected from glycemic control are discussed in detail in the guideline.

Outcome Estimates: Mathematical models have been developed to provide estimates of the magnitudes of the benefits and harms of glycemic control for individual patients. For example, a model based on data from the DCCT and other sources estimated that patients with type 2 diabetes who maintained a glycated hemoglobin level of 7.2% would reduce the cumulative incidence of blindness, end-stage renal disease, and lower extremity amputation by 72% (from 19% to

5%), 87% (from 17% to 2%), and 67% (from 15% to 5%), respectively. Life expectancy would increase by 1.39 years. Using a Markov model based primarily on the DCCT, another group of investigators estimated that reducing glycated hemoglobin from 9% to 7% in a patient in whom diabetes developed at age 45 would lower the lifetime risk of blindness from 2.6% to 0.3%. The same change in a patient with diabetes onset at age 65 would decrease the risk of blindness from only 0.5% to less than 0.1%. Accordingly, a physician might approach patients in these age groups very differently, especially if the 65 year-old person already had a complication of diabetes or a major comorbid disease.

Ideally, these modeling data could be used to develop outcome tables that clinicians and patients could consult to estimate the benefits and harms of different levels of glycemic control for individual clinical scenarios. Available models, however, produce discrepant results about the likely outcomes of glycemic control in the same patient. For a 55-year-old Caucasian patient who lowers his or her glycated hemoglobin level from 9% to 7%, for example, the Eastman model estimates that the lifetime risk of blindness would be reduced from 9% to 3.4%, whereas the Vijan model estimates that it would be reduced from 1.2% to 0.1%. Accordingly, the absolute risk reduction for this scenario differs considerably between the Eastman and Vijan models (5.6% versus 1.1%, respectively).

Some of these discrepancies relate to fundamental differences in the design, assumptions, and data employed in the models. Investigators are currently updating their models to address these discrepancies, with the ultimate goal of producing explicit outcome tables that patients and clinicians can use to estimate the likely outcomes of glycemic control.

POTENTIAL HARMS

Specific complications in addition to hypoglycemia can occur with each of the agents used to treat type 2 diabetes. As with most pharmaceuticals, insulin has potential adverse effects and oral drugs to reduce glycemia (sulfonylureas, metformin, acarbose) carry some risk of undesirable side effects (e.g., flatulence, diarrhea) and highly uncommon, more serious complications (e.g., lactic acidosis, hepatotoxicity). A detailed listing of all potential side effects of diabetic medications and of their reported probability rates is beyond the scope of the guideline.

Hypoglycemia

Evidence about the magnitude and statistical significance of the risk of hypoglycemia and its complications is inconsistent across clinical trials. Furthermore, the risk of severe hypoglycemia appears to differ between patients with type 1 and type 2 diabetes, being greater in the former and therefore not reviewed here. Some trials involving patients with type 2 disease reported an increased risk for minor hypoglycemic episodes. In the Veterans Administration trial, the incidence of mild to moderate hypoglycemia (16.5 versus 1.5 patients/year) was greater in patients receiving intensive treatment ($p < 0.001$), but the incidence of severe episodes was low and did not differ significantly.

In the United Kingdom Prospective Diabetes Study (UKPDS), the incidence of major hypoglycemic episodes was higher among intensively treated than among conventionally treated patients ($p < 0.0001$), but the rates were low in both groups (1-2% versus 0.7%, respectively). The incidence of any hypoglycemic episode, including minor events, was higher among intensively treated patients than among controls. Among those taking insulin, each year about 3% had a major episode and 40% a minor or major episode. There was only one death from hypoglycemia in 3867 patients followed over 10 years.

A recent cohort study of 8668 patients with type 2 diabetes provides data from community practice at a large health maintenance organization. Although patients taking sulfonylureas were no more likely to report symptoms attributed to hypoglycemia (e.g., sweating, weakness, trembling, insulin reaction) than those not receiving hypoglycemic medications, 17% of patients receiving insulin reported that such symptoms occurred weekly. Thirty-eight percent reported that hypoglycemic symptoms occurred at least two to three times per month; 23% reported never having such symptoms. Insulin therapy was not associated with increased emergency department visits or hypoglycemia-related hospitalizations.

Weight gain

Several trials have reported and association between intensive treatment and weight gain. The Diabetes Control and Complications Trial (DCCT) noted a 33% increase (12.7 versus 9.3 cases/100 patient-years) in the risk of becoming overweight (20% greater than desirable body weight). At five years, patients in the intensive treatment group had gained an average of 4.6 kg more than those receiving conventional therapy. In the Oslo Study, body weight over 2 years was higher in the multiple injection group than in the continuous and conventional treatment groups. In the UKPDS, weight gain was and average of 3.1 kg higher among patients intensively treated with insulin or sulfonylureas than among controls. There is no evidence that this amount of weight gain in an obese individual significantly impacts on outcomes. In fact, the intensively treated patients in the UKPDS appeared to have borderline improvement in some cardiovascular outcomes.

Other adverse effects

Intensive glycemic control generally requires patients to closely monitor their blood glucose levels at home, often on a daily basis; follow careful dietary restrictions and increased physical activity; tolerate minor side effects and the risk of more serious complications from medications; visit the doctor on a regular basis for testing and examinations; and absorb out-of-pocket costs not covered by insurance for physician services and medical supplies, lost work (or school) time, and transportation. Although the influence attributable to insulin versus glycemic control is unclear, a cohort study found that insulin users had more laboratory tests performed, 2.4 more outpatient visits per year, and almost 300 more fingersticks for home glucose monitoring than patients using sulfonylureas. In many cases these inconveniences, discomforts, and costs must be borne over a number of years, often a lifetime. There are currently few reliable data on which to measure the magnitude of these problems, their relative importance to patients, or the degree to which they are offset by the benefits of treatment. The DCCT found no association between intensive treatment and lower quality of life.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

These recommendations are provided only as an assistance for physicians making clinical decisions regarding the care of their patients. As such, they cannot substitute for the individual judgment brought to each clinical situation by the patient's family physician. As with all clinical reference resources, they reflect the best understanding of the science of medicine at the time of publication, but they should be used with the clear understanding that continued research may result in new knowledge and recommendations.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

American Academy of Family Physicians, American Diabetes Association. Controlling blood glucose levels in patients with type 2 diabetes mellitus. J Fam Pract 2000 May;49(5):453-60. [110 references]

American Academy of Family Physicians. The benefits and risks of controlling blood glucose levels in patients with type 2 diabetes mellitus. A review of the evidence and recommendations American Academy of Family Physicians, American Diabetes Association. Leawood (KS): American Academy of Family Physicians (AAFP); 1999 Apr.

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1999 Apr

GUIDELINE DEVELOPER(S)

American Academy of Family Physicians - Medical Specialty Society
American Diabetes Association - Professional Association

SOURCE(S) OF FUNDING

The systematic review on which this guideline is based was supported in part by funding from the Health Care Financing Administration.

GUIDELINE COMMITTEE

Diabetes Policy Team

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

The panel was composed of family physicians, general internists, endocrinologists, and a practice guidelines methodologist, some of whom were appointed by the American Diabetes Association and American College of Physicians-American Society of Internal Medicine.

Members: Steven H. Woolf, MD, MPH; Mayer B. Davidson, MD; Sheldon Greenfield, MD; Hanan S. Bell, PhD; Theodore G. Ganiats, MD; Michael D. Hagen, MD; Valerie Anne Palda, MD, MSc; Robert A. Rizza, MD; Stephen J. Spann, MD

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

The report was reviewed by a panel of outside experts and family physicians, and revisions consistent with the panel methodology were incorporated. The final report was approved in March 1999 by the respective Boards of the American Academy of Family Physicians and the American Diabetes Association.

An update is not in progress at this time.

GUIDELINE AVAILABILITY

Electronic copies: An HTML Text version is available American Academy of Family Physicians (AAFP) Web site.

Also available (in Portable Document Format [PDF]) from the American Academy of Family Physicians (AAFP) Web site.

Print copies: Available from AAFP, 11400 Tomahawk Creek Parkway, Leawood, KS 66211-2672.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on September 15, 2000. The information was verified by the guideline developer as of January 31, 2001.

COPYRIGHT STATEMENT

Date Modified: 11/15/2004